Remarks

Priority Claim

The priority claim has been amended to recite the relationship with the prior applications (continuation, continuation in part, priority under 35 USC 119), as well as to insert the second issued patent number.

Double Patenting

With respect to claims 1-16, these have been amended to recite a "column" in the independent claim. This should remove the double patenting rejection over U.S. Patent No. 6,231,536, which requires in all of the claims the limitation that the blood is treated to remove molecules having a molecular weight of 120,000 daltons or less. No such limitation is present in the pending claims. Antibodies do not separate based on molecular weight.

Although the undersigned strongly disagrees with the examiner's conclusions regarding double patenting, and that such terminal disclaimers improperly deprive applicant of the extension of time during the period this application may be involved in an interference, appropriate terminal disclaimers are included to overcome the rejections for obviousness type double patenting over U.S. Patent No. 6,231,536, 6,620,382 and 09/699,003, and thereby facilitate prosecution.

With respect to claims 17-22, these claims were copied from U.S. Patent No. 6,379,708 to Howell, et al. and are properly the subject of an interference, not a double patenting rejection, since the award of these claims will depend on the outcome of the interference proceedings. Proper support for each of these claims was previously provided and they issued on a much later filed application.

The basis for the claims as originally presented is indicated in the claims as shown below in bold. The basis as found in Applicant's May 22, 1998, application is also shown below in italics.

17. A method of enhancing an immune response in a patient **(page 1, lines 6-7)** comprising:

a. obtaining whole blood from the patient **(page 18, lines 4-8)**; *(page 6)*

b. separating out the plasma. **(page 18, lines 7-8)**; *(page 6)*

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor **(page 18, lines 8-11; page 6, lines 1-7)**; *(page 11, lines 23-26)*

d. removing the inhibitor bound to the antibody from the plasma **(page 18, line 8-11)**; *(page 11, lines 23-26)* and

e. returning the antibody-contacted plasma to the patient. **(page 18, lines 11-15).** *(page 7)*

18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane. **(page 9, lines 1-5)** *(page 11, lines 27-28)*

19. The method of claim 17, wherein the antibody is recombinant or a binding fragment. **(page 6, lines 18-20).** *(page 11, lines 24-26)*

20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor. **(page 6, line 27)** *(page 11, lines 22-29)*

21. The method of claim 17, wherein the patient is human. **(page 6, line 26).** *(examples)*

22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta. *(page 11, lines 22-29)*

Rejections under 35 U.S.C. 112

Claims 17-21 were rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

Claim 17 was rejected for using the term "targeted immune system inhibitor". It should be noted, on the record, that this is the language used in the copied Howell patent, based on no more disclosure than what is present in applicant's specification. However, to moot this point, and since the examiner has acknowledged there is written support for the term "soluble cytokine receptors" this language has been inserted into claims 17 and dependent claim 22. With respect to the statement that the application is limited to molecules produced by tumors, the examiner is mistaken. Attention is drawn to the application at page 3, lines 1-4, which states "such as many types of cancer, and certain diseases such as HIV, where the disease immunosupresses the patient". See also page 6, line 1, and page 21, lines 20-26. Actual working examples of treatment of autoimmune disease may be found in applicant's other application, now U.S. Patent No. 6,620,382.

Claim 18 has been amended to correct the grammatical error.

Claims 1-3, 5, 8-11, and 17-22 were rejected under 35 U.S.C. 112, second paragraph as indefinite.

Claim 1 has been rejected for use of the phrase soluble cytokine receptor molecules at line 5 and with respect to the phrase "binding". Claim 1 has been amended to use Markush language, which should obviate any indefiniteness, as well as amended to correct grammatical basis.

Claim 17 has been amended to clarify antecedent basis, although it is believe this has previously been rendered moot.

It is not understood what the problem is with either of claim 5 or 8. Claim 5 requires a second type of treatment, as demonstrated by the examples in the application. The treatment method of claim 5 is used with the treatment of claim 1. This may be before, during or after the treatment of claim 1. Claim 8 is simply the method of claim 1 using the first group present in the Markush claim (the antibodies or antibody fragments).

Claim 19 has been amended to delete the reference to fragments, and fragments added to claim 17, from which it depends.

Rejection under 35 U.S.C. 102(e)

Claims 1, 8, 9 and 11 were rejected under 35 U.S.C. 102(e) as disclosed by U.S. Patent No. 5,817,528 to Bohm. This rejection is respectfully traversed.

Claim 1 reads as follows:

A method for reducing the amount of transformed, infected or diseased tissue in a patient comprising

contacting the blood, plasma or one or more components of the blood of a patient in need thereof with a column having immobilized therein an effective amount of soluble cytokine receptor inhibitors selected from the group consisting of antibodies or antibody fragments binding to soluble cytokine receptor molecules, and soluble cytokine molecules, wherein the cytokine receptor is selected from the group consisting of soluble tumor necrosis factor receptor-1 ("sTNFR-1") and soluble tumor necrosis factor receptor-2 ("sTNFR-2"), wherein binding of the soluble cytokine receptor inhibitors prevents soluble cytokine receptors from binding to cytokines in the tissue to be treated, until the transformed, infected, or diseased tissue is reduced in amount compared to the amount present at the time the treatment is initiated.

Bohm discloses using immobilized antibodies to remove molecules such as antibodies from the plasma.

The examiner has provided an interesting interpretation of the phrase "soluble cytokine receptor". This is not the definition provided in the application by means of examples, nor the art recognized definition. A search of the internet for definitions provides the following:

sCR

abbr. for soluble cytokine receptor. Many receptors for cytokines exist in membrane-bound and soluble forms (see also: Receptor shedding). Soluble cytokine receptors arise by proteolytic cleavage of transmembrane receptors or by utilisation of alternatively spliced receptor mRNAs. They may participate in the control of cytokine activity in vivo by preventing from binding to their membrane receptors. This type of interactions is the basis of a growth control mechanism termed retrocrine . Soluble cytokine receptors acting as cytokine inhibitors in vitro and in different experimental models are characterizeed by their specificity, high affinity, and low immunogenicity. They are of interest as immunotherapeutic agents. Some of these receptors have been used as antibody fusion proteins , known as immunoadhesins (see: Etanercept). See also: Cytokine receptor families .

date of last revision: January 2002

References: Fernandez-Botran R Soluble cytokine receptors: novel immunotherapeutic agents. Expert Opinions in Investigative Drugs 9(3): 497-514 (2000)

CYTOKINE RECEPTORS (SOLUBLE) - serum

Specimen: 5 mL blood in plain tube.

Method: Immunoassay or bioassay.

Reference Interval: Method dependent.

Application: These analytes have no proven role in the diagnosis or monitoring of disease.

Interpretation: Detected in a broad range of inflammatory, infectious and malignant disorders.

Reference: Steiner G *et al. J Rheumatol* 1995; 22: 406-412. Stasi R *et al. Eur J Hematol* 1995; 54: 9-17.

Cytokines (Chapter 12 of Immunology: fifth edition)
CYTOKINES, PROPERTIES AND FUNCTION
Soluble Cytokine Receptors

Receptors may occur in soluble forms which typically retain high affinity for the cytokine and thus are capable of binding the cytokine with in solution. One of two main mechanisms results in solublization:

1. proteolytic cleavage of the extracellular domain, releasing the receptor from the cell membrane. This is often a result of some specific activation event acting on the cell; for example the M-CSF receptor is cleaved from the cell surface by a protease induced by the activation of protein kinase C. Also, the TNF receptors, p55 and p75 are solublized by this mechanism. In fact it appears that solublization of p75 can occur following binding of TNF to p55.
2. splicing out of the transmembrane encoding exon of the primary RNA transcript resulting in a protein that is secreted, and not anchored in the plasma membrane. Examples of cytokine receptors that are solublized by this mechanism includes IL-1, IL-4, IL-7, some of which appear to occur constitutively, and perhaps not due to specific activation signals.

Mechanism/roles of soluble receptors include ***[Figure from Blood 87:847-857, 1996]***:

1. receptor down-regulation; the receptor can no longer serve as the signaling molecule to the cell, limiting the response of the cell to the cytokine ligand
2. the soluble receptor may become a binding protein that protects the ligand from degradation or clearance in the extracellular space. The receptor now has no role in signaling but facilitate the delivery of the ligand to additional membrane-bound receptors.
3. the soluble receptor binds to the cytokine preventing it from binding further membrane-bound receptors- becoming a direct antagonist. Examples include the IL-1, IL-4 and TNF receptors.
4. Receptor families consisting of multichain receptors, such as the IL-6R family, binding of the soluble alpha receptor chain to the ligand can confer sensitivity to another cell which may have only the beta chain (gp130). This greatly expands the number and types of cells sensitive to the soluble receptor/ligand complex.

CHEMOKINE RECEPTOR FAMILY - from IMMUNOLOGY by Kuby© 1992, 1994, 1997 by W.H. Freeman and Company. Used with permission

The chemokine receptors are members of a superfamily of seven transmembrane loops and transduce their signals through heterotrimeric G proteins.

Chemokine receptors are structurally related and can be categorized into *specific* (bind only one known ligand - e.g., CXCR1/IL8RA and CXCR4/fusin/LESTR), *shared* (CXCR2/IL8RB, CXCR3, CCCR1-CCCR5), *promiscuous* (bind to many chemokine ligands of either CXC or CC types - e.g. Duffy blood group antigen), and *viral* (shared receptors that have been transduced into viral genomes during evolution - herpes saimiri virus and cytomegalovirus). As might be expected, some chemokine receptors are structurally related. For example, CXCR1 and CXCR2 receptors are approximately 65% identical. The N-terminal portion of chemokine receptors is key to determining ligand binding specificity.

If engagement of chemokine receptors results in the movement of the cell, a complex series of signaling circuits are involved. Different pathways lead to activation and proliferation.

Clearly it is necessary that there be mechanisms by which cytokines are downregulated. Examples include:

(1) Cytokine antagonists such as the IL-1 receptor antagonist (IL-1Ra) which binds to the IL-1 receptor. Antagonists bind to a specific receptor but do not transmit a signal. Production of IL-1Ra appears to play a role in regulating the intensity of the inflammatory response.

(2) Soluble cytokine receptors can be found in the blood and extracellular fluid. These soluble receptors result from enzymatic cleavage of the extracellular domain of cell-bound cytokine receptors. The released soluble fragments can bind cytokine molecules, thereby neutralizing their activity. The soluble IL-2 receptor (sIL-2R) , which is released following chronic T cell activation is the best characterized. The shed receptor can bind IL-2 and prevent its interaction with the membrane-bound IL-2R.

(3) Other cytokines, acting through quite separate receptors, could exert opposite effects on cells.

(4) Cytokines could bind to receptors that do not activate the cell.

Cytokine antagonists are being considered for use as treatments for diseases associated with overproduction of cytokines - such as bacterial septic shock (gram negative bacteria with overproduction of TNF-a or IL-1) or bacterial toxic shock (bacterial superantigens with overproduction of TNF-a or IL-1).

As is clear from the foregoing, the art recognized definition of the term "soluble cytokine receptor" does not include antibodies to the receptors, but only to endogenous soluble cytokine receptor. The Courts have made it clear that if there is any ambiguity on the face of the claims, then one looks first to the specification (which in this case provides examples consistent with the above-articles) and then to the art recognized definition. The foregoing extracts make it quite clear that this phrase does not encompass the molecules described by Bohm, et al. since Bohm discloses antibodies immobilized on a column, but only anti-antibodies and anti-cytokine antibodies, which is not encompassed by the claims. The claims define a column having immobilized thereon antibodies or antibody fragments which are reactive with soluble cytokine receptors OR soluble cytokine receptors.

Rejection under 35 U.S.C. 103

Claims 10 and 17-21 were rejected under 35 U.S.C. 103 as obvious over Bohm in vewi of U.S. Patent No. 4,512,763 to Schneider and further in view of U.S. Patent No. 5,565,332 to Hoogenboom, et al. This rejections is respectfully traversed.

Bohm is discussed above. As noted above, Bohm does not disclose immobilized antibodies reactive with soluble cytokine receptors nor immobilized soluble cytokines to remove soluble cytokine receptors, nor does the disclosure of Bohm lead one of ordinary

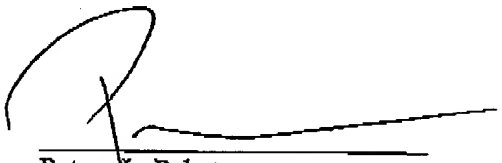
skill in the art to use such materials, much less with a reasonable expectation of success. Neither Schneider nor Hoogenboom make up for this deficiency.

While it is possible that the copied claims from U.S. patent No. 4,512,763 to Howell have a broader meaning, the claims in **this** application must be read in view of **this** specification and according to how those of ordinary skill in the art would read the claims. This would not be as the examiner is alleging. The claim language does not encompass removing soluble antibodies to cytokine receptors using antibodies to the antibodies which have been immobilized on a column.

The foregoing extracts also make it clear that it is not obvious such a method would be efficacious - indeed, the art indicates that it would not be obvious and one skilled in the art would not have expected such a method to be effective.

Claims 1-3, 5, 8-11, and 17-22 are definite, comply with the written description, and novel and non-obvious over the prior art. As such, they should be allowable.

Respectfully submitted,



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